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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LUNDGREN, JEFFREY S	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 05/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/908,943	YAN ET AL.	
	Examiner	Art Unit	
	Jeff Lundgren	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *102-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *102-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Following Applicants' Reply filed on February 28, 2006, claims 102-131 are pending in the application; an action of the merits of claims 102-131 is provided for below.

Withdrawn Objections and Rejections

Objection to Title Overcome by Applicants' Amendment

The objection to the title is overcome by Applicants' amendment.

Claim Objections

The objection to claim 130 is for the typographical error "t transgenic," has been overcome by Applicants' amendment.

Claim Rejections - 35 USC § 112, second paragraph

The rejections of claims 102-131 under 35 USC § 112, second paragraph, are withdrawn in view of Applicants' amendments and arguments presented in the Reply filed on February 28, 2006.

Claim Rejections - 35 USC § 102

The rejection of claims 102-115, 117-121 and 123-131 under 35 U.S.C. 102(e) as being anticipated by Fang *et al.* ("Fang"), U.S. Patent Appl Pub. No. 2003/0096864 A1, are withdrawn for the reasons argued by Applicants.

Claim Rejections - 35 USC § 103

The rejection of claims 102-115 and 117-131 under 35 U.S.C. 103(a) as being unpatentable over Fang and Zhang et al. ("Zhang"), U.S. Patent No. 6,248,904, is withdrawn for the reasons argued by Applicants.

Maintained Claim Rejections

Claim Rejections - 35 USC § 112, first paragraph (written description)

The rejection of claims 102-109 and 117-131 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants' reply has been fully considered, but is not found persuasive.

Applicants allege that the rejection of the claims for lack of written description is improper. Applicants contend that the genus as set forth in the Application is not overly broad in view of the fields chemistry and biology (Reply, page 12), that the 48 species in the specification supports their claim breadth, and argue the Gruninger-Leitch reference is not on point. Applicants also allege that there claims exclude all inoperable embodiments of the reference, and that their compounds are cleaved at a useful rate.

In reference to the Gruninger-Leitch reference, Applicants allege that their claims exclude all inoperable embodiments of Gruninger-Leitch, and that their claims substrates all are cleaved at a useful rate. This is not persuasive, because although Applicants' have descriptive support for certain embodiment of the claims, Applicants do not have descriptive support for the full breadth. Therefore, the written description rejection only applies to certain claims, *i.e.*, not the operative embodiments, and not the compositions cleaved at useful rates.

As stated before, certain factors identified in Gruninger-Leitch's teachings would suggest that Applicants' claimed genus is unsupported by their disclosure include the following factors: i) the effects of, and importance, of amino acids further from the scissile bond of the substrate, such as P_4, P_3, $P_{3'}$ and $P_{4'}$; ii) the length of the substrate required for cleavage by the BACE enzyme; and iii) certain *in vitro* and *in vivo* differences in activity, wherein any single factor may or may not be coupled to any other factor(s). Table 1 illustrates the effects of certain substrate mutations compared to the Swedish type APP substrate. A single amino acid mutation at P1' of the Swedish mutant APP β-cleavage site (NL-D → NL-A), results in an 84% drop in activity. Even more surprisingly, the P4K substrate which differs from the Swedish mutant APP β-cleavage site (NL-D) by a single amino acid at P_4, yet retains the same P_2P_1-$P_{1'}P_{2'}$ sequence,

results in a 50-fold drop in activity (Table 1 on page 4689). These mutations and effects are relevant to the breadth and subject matter of Applicants' claims, and do not appear to be remedied by the art or Applicants' disclosure.

Furthermore, Applicants have taken the argument out of context. The argument does not merely rely on a single reference, such as Gruninger-Leitch's teachings, but many teachings that combined show strong evidence that Applicants did not possess the full breadth of the genus.

Applicants further allege that neither *Lily* or *Enzo* support the Examiners position that the claims do not have written description support for the full breadth. Regarding *Lily*, Applicants content that the generic limitations of the instant claims is different, namely a number of species support a genus formula, whereas *Lily* did not have a genus. Regarding *Enzo*, Applicants allege that their 48 species is sufficient to support the claimed subject matter by its function.

Neither argument is persuasive. Regarding *Lily*, the point the court set forth is that the species should reasonably support the genus, regardless of a generic chemical representation. The substantial evidence of related art presented by the Examiner directly addresses why the 48 species extends beyond an art-accepted genus. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1983), the court communicated that the question regarding written description is whether the specification "reasonably conveys to the artisan that the inventor had possession." Generally, Applicants species are more focused and limited to certain amino acid combinations when viewed in comparison to the claimed breadth (for example, the repeat theme of the amino acid sequence SYEV is common; also see Tables 2-5 regarding other sequence themes). However, certain of Applicants' claims, such as claim 102, are not commensurate in scope with Applicants species when considered in view of the teachings in the art. Just because an amino acid works in one sequence with substantial variations at other positions, does not necessarily make it part of an accepted genus in any other combination or permutation of sequences as Applicants appear to suggest. The art cited by the Examiner presents a sufficient showing backing the Examiner's position on this point, many of which were not reasonably addressed or rebutted by Applicants.

Regarding Applicants' arguments pertaining to the holding in *Enzo*, the same arguments in the aforementioned paragraph apply.

Applicants further contend that the written description rejection as set forth by the Examiner focuses on unpredictability, and is more appropriate for an enablement rejection (Reply, page 16, first paragraph).

Applicants also argue that they are entitled to certain inoperative embodiments within the claims, and cite *Atlas Powder Co. v. E.I. Du Pont de Nemours & Co. Inc.* 750 F.2d 1569 (Fed. Cir. 1984), wherein the legal determination hinges on the number and/or significance of the inoperative embodiments.

While the Examiner agrees with the general principle noted by Applicants in *Atlas Powder*, Applicants' points miss the mark. Specifically, Applicants are not entitled to inoperative embodiments where the art suggests certain boundaries between the operative and inoperative embodiments exist. For example, in *Lily*, there was a strong showing of evidence that the species did not support certain inoperative embodiments.

Applicants argument regarding attention to "unpredictability" is also not found persuasive. The art cited by the Examiner exemplifies how the genus breadth that can be supported by certain species as described below.

As stated in the previous Office Action, the fact that the amino acid substitution effects are not necessarily additive, and that drastic effects in activity can be observed by changing amino acids either in the P_2P_1-$P_1'P_2'$ region, support for Applicants' genus is reasonably challenged by the teaching of Leitch. As a result of each of these factors, considered independently or as having a cumulative effect on the substrate/enzyme relationship, one of ordinary skill in the art would doubt that Applicants had adequately described the invention as broadly claimed.

Tomasselli also reports experimental findings that demonstrate that the claimed genus is not supported by the disclosed species because of amino acid interdependence and *in vitro* and *in vivo* differences in activity:

> "Enzyme subsites are interdependent and occupancy of a subsite by two 'well tolerated', but different amino acids, may differentially influence the amino acid preferences at the other subsites."

Tomasselli at page 1014, column 1; and again regarding the interdependence of amino acids:

> "Our findings indicate that amino acid preference at a specific site has to be regarded in the context of the peptide sequence rather than of maximal statistical occurrence of that amino acid at that specific position in the substrate. *A P1 Leu may be highly preferred in a library of peptide substrates, but Tyr is optimal at this position in our best substrate because of its interdependence upon its neighboring P-site substituents.* We have produced an optimal BACE1 substrate by systematic changes in individual P-sites considered globally with respect to the overall sequence, and by N-terminal extension of the peptides with the naturally occurring APP sequence."

Id. at page 1014, column 2 (emphasis added). Regarding Tomasselli's "systematic" approach, however, neither Applicants nor Tomasselli provide sufficient description to link all of the claimed species to the genus. Instead, one of ordinary skill in the art would consider the approaches of Leitch and Turner to be "systematically" different, but still systematic. For example, Shi discloses a BACE substrate identified by a library approach that is about 3-4 fold scissile than that disclosed by Tomasselli (Shi at page 141, column 2). Although certain approaches may be better served for identifying a few particular species, Applicants' and Tomasselli's approaches do not sufficiently describe the breadth of the genus as claimed.

Majer discloses a series of compounds produced through a systematic approach for optimizing inhibitor polypeptides to cathepsin D, an aspartic protease. Similar to optimizing BACE substrates with a scissile bond, a number of factors are important in substrate/inhibitor optimization, including but not limited to, hydropathy, orientation of the amino acid side chains, backbone configuration, hydrogen bonding, side chain length, and a number of subsite considerations, such as steric interactions, solvation, etc. Majer also teaches that there are additional important considerations besides the P_2P_1-$P_1'P_2'$ amino acid residues (pages 1458-1465), and that amino acid substitutions are not necessarily additive (page 1462).

Many of the claimed amino acid substitutions do not necessarily follow from any disclosure, or the corresponding systematic approaches. One sequence that only differs from Applicants' most active substrate (SY-EV) is the sequence GY-EV as disclosed in Sauder (see Figure 4 on page 246, and description thereof on page 245), however, this sequence has drastically reduced in activity in comparison. Based on the hydropathic index, the single value difference between S → G is –0.4 (see page 110 of Kyte and Doolittle, *J. Mol. Biol. 157(1)*:105-

132 (**1982**)). Vassar discloses that a substitution of a single amino acid to P1 of the APPwt (M → V), results in elimination of the scissile bond. Although the difference in going from M → V has a single position value difference in the hydropathic index of 2.3, the wt to Sweedish mutation has a hydropathic difference of comparable magnitude at 2.0 at P1 (Kyte at page 110).

P_2P_1-$P_1'P_2'$ Sequence	***Description***
KM-DA	APPwt
NL-DA	Swedish mutant with high increase in activity
KV-DA	lacks activity
GY-EV	low activity; the wt β'-secretase site
SY-EV	Applicants' most active sequence fragment
NF-EV	Shi's most active sequence fragment

However, it is not truly clear from Applicants' or any other "systematic" approach, or the teachings in the art, what effects certain amino acid substitutions will have on a substrate, even if the substitution is sometimes preferred for one particular substrate, or by relying on hydropathic indexing.

Accordingly, for at least these reasons, Applicants have not adequately described the invention for the breadth that is claimed. It thus appears that Applicants were not in possession of the claimed invention at the time the application was filed, the structure-function relationship between the protease and the scissile substrates have not been adequately set forth, and that Applicants' species do not support the claimed genus.

The rejection is maintained.

Claim Objections

Claims 110-116 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

New Grounds of Rejection Necessitated by Applicants' Amendments in Certain Related U.S. Applications

Double Patenting

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. § 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 102-131 are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 84-107 of copending Application No. 10/801,493. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claims 102-131 are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 84-107 of copending Application No. 10/801,509. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claims 102-131 are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 84-107 of copending Application No. 10/801,938. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusions

No claim is allowable.

If Applicants should amendment the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JSL

PETER PARAS, JR.
PRIMARY EXAMINER

SPE 1639